2001 National Survey of Hospital Coagulation Laboratory Practices:
Testing for Prothrombin Time (PT), Activated Partial Thromboplastin Time (aPTT) and Low Molecular Weight Heparin (LMWH)

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Introduction

Hospital clinical laboratories play an important role in healthcare; and as documented in this survey, an estimated 97% of hospital laboratories reported performing coagulation tests. Coagulation tests are known to be vital to the diagnosis, treatment and management of bleeding and hypercoagulability disorders, and the majority of them are performed to screen for coagulation disorders or to monitor therapeutic anticoagulant therapy. In response to the uncertainty surrounding coagulation testing practices, we conducted this survey of hospital coagulation laboratories in the US, and chose hospitals as the testing environment to address a broader spectrum of in-house testing practices not subject to observation in physician office laboratories or other point-of-care testing sites. The purpose of this survey was to evaluate the availability of coagulation tests, assess various pre-analytical, analytical and post-analytical stages of the testing process, and evaluate some testing practices critical to clinical management of patients. This paper presents reported practices relating to testing for prothrombin time (PT), activated partial thromboplastin time (aPTT) and low molecular weight heparin (LMWH).
The survey used and a summary of our findings can be found at http://www.phppo.cdc.gov/mlp/coag2001.asp.

Methods

A group of coagulation laboratory experts and survey methodologists assisted the CDC in the development as well as the evaluation of the content and format of this 2001 survey of hospital coagulation laboratory directors (response rate, 79%). Furthermore, several versions of the survey were pilot tested in 9 hospital coagulation laboratories before its final dissemination. From a sampling frame of institutions listed in the 1999 directory of the American Hospital Association (AHA), we randomly selected 800 hospitals (sampling rate, 14%), and assessed practices in their coagulation laboratories. This sampling frame is not limited to the AHA members and it includes 95% of all hospitals as indicated by the Online Survey, Certification and Reporting database of CLIA-registered hospital laboratories. Participants had the option of responding via Internet, and 20 (3%) did so. Inconsistent responses were excluded from data analysis.

Results

Response rate. We received returned surveys from 632 institutions, resulting in a response rate of 79%.

Performance of coagulation tests
Of the 629 responding to this question, 612 (97%) reported performing coagulation testing.

Prothrombin Time (PT) Testing Practices

Performance of PT assay
Of the 605 respondents providing valid responses, 100% noted performing the PT assay.

Anticoagulant concentration
- 73% (n = 437) reported using 109 mmol/L (3.2%) sodium citrate.*
- 25% (n = 156) reported using 129 mmol/L (3.8%) sodium citrate.
- 1% (n = 8) reported using both concentrations.

*Based on the recommendation of the World Health Organization (WHO) and NCCLS, 109 mmol/L (3.2%) citrate is the anticoagulant of choice (*Arch Pathol Lab Med*. 1998;122:768–781). Under-filling of specimen tubes containing 3.8% sodium citrate has been reported to prolong PT and especially aPTT results compared to 3.2% sodium citrate (*Am J Clin Pathol*. 1998;109:754-757) — potentially affecting decisions about anticoagulant therapy with its consequent implications for patient outcome.

Reporting of results (n = 626)*
- 99.8% reported PT as international normalized ratio (INR).
- 97% reported PT in seconds.
- 16% reported PT as a therapeutic PT ratio.
- 3% reported PT as INR only.

*Of those responding to this question, 1 respondent (0.02%) noted reporting PT results in units other than INR (in this case, the respondent reported results in seconds and as therapeutic PT ratio). Reporting PT results in seconds only may lead clinicians to inappropriately compare results between institutions (*Am J Clin Pathol*. 1998;109:589–594) and reliance on PT therapeutic ratio has been documented to cause errors in anticoagulant therapy (*Arch Intern Med*. 1992;152:278–282).

Establishment of reference interval for PT assay
Of the 576 valid responses, 531 respondents (92%) reported they conducted in-house evaluations to establish reference intervals for their PT assay. In-house establishment of the PT reference interval was based on the following minimum number of subjects:*
- ≤20, 16% (n = 86);
- 21-39, 43% (n = 235);
- 40-59, 23% (n = 128);
- 60-119, 14% (n = 74);
- 120-199, 3% (n = 15);
- ≥200, 2% (n = 9).

*To establish a reference interval, the NCCLS has recommended a minimum of 120 subjects for each reference population or subclass as the smallest number allowing determination of a 90% confidence interval around reference limits [NCCLS. *How to Define and Determine Reference Intervals in the Clinical Laboratory*; Approved GuidelineSecond Edition (Document C28-A2). Wayne, PA:NCCLS; 2000].

Sensitivity of PT assay to heparin
- 17% (n = 100) reported determining sensitivity of their PT assays to heparin.
- 50% (n = 271) reported selecting a PT-thromboplastin reagent that was insensitive to heparin in the heparin therapeutic range.

According to the College of American Pathologists (CAP), laboratories should determine the sensitivity of their PT assays to heparin (*Arch Pathol Lab Med*. 1998;122:782–798) and, where possible, select a thromboplastin that is insensitive to heparin in the therapeutic range (*Arch Pathol Lab Med*. 1998;122:768–781).

International sensitivity index (ISI) of thromboplastin lot
The ISI of the respondents' current thromboplastin lot was 0.89-2.63 (average, 1.60; median, 1.81).
- 44% (n = 247) reported ISIs of ≤ 1.70.*
- 34% (n = 190) reported ISIs of ≤ 1.20.*

*The CAP recommends ISIs of ≤ 1.70 (*Arch Pathol Lab Med*. 1998; 122:768-781) while the American College of Chest Physicians recommends ISIs of ≤ 1.20 [*Chest*. 1995;108(4 Suppl):231S-246S].

Activated Partial Thromboplastin Time (aPTT) Testing Practices

Performance of aPTT assay
Of the 608 respondents, 601 (99%) reported performing aPTT assay.

Heparin therapeutic range
64% (n = 355) reported having an aPTT therapeutic range for heparin.
While 64% (n = 231) of those having an aPTT therapeutic range for heparin reported this range when monitoring heparin therapy, 9% (n = 33) included the corresponding heparin concentration with aPTT results.

How the aPTT therapeutic range for heparin was determined
The respondents did the following to determine the aPTT therapeutic range for heparin.*
- Used samples from patients on heparin therapy to compare a new reagent lot to an old reagent lot, 59% (n = 173).
- Used heparin spiked samples to compare a reagent lot to an old reagent lot, 46% (n = 130).
- Used samples from patients on heparin therapy to compare a new heparin lot to an old heparin lot, 15% (n = 41).
- Used heparin spiked samples to compare a new heparin lot to an old heparin lot, 12% (n = 33).

*The aPTT therapeutic range for heparin should be determined by comparing (1) ex vivo specimens with an appropriately validated heparin assay (preferably) or (2) ex vivo specimens to a previously calibrated aPTT using a method to control for reagent drift (*Arch Pathol Lab Med*. 1998;122:782-798). Equivalence should be determined by using ex vivo plasma samples obtained from patients treated with unfractionated heparin rather than spiked in vitro heparinized plasma samples (*Am J Clin Pathol*. 1985;84:351-354).

Reconfirming aPTT therapeutic range for heparin*
Of the 357 respondents, the following proportions reconfirmed the aPTT therapeutic range:
- 79% when new instrumentation was used,
- 75% when new reagent lots were used,
- 51% when new reagents were used, and
- 47% when new instrumentation, new reagent lots or new reagents were used (47%).

*Current consensus maintains that therapeutic ranges should be recalculated after the introduction of a new reagent, a new lot of the same reagent, or a change in instrument (*Arch Pathol Lab Med*. 1998;122:782-798).

Pre-analytical specimen management
- 96% (n = 535) reported assaying specimens within 4 h after phlebotomy.*
- 88% (n = 467) reported centrifuging specimens within 1 h of collection.*
- 82% (n = 419) reported keeping specimens at room temperature.
- 22% (n = 101) reported keeping specimens at 4 °C.

*According to NCCLS, samples can be assayed up to 4 h after phlebotomy if centrifuged within 1 h of collection [NCCLS. *Collection, Transport and Processing of Blood Specimens for Coagulation Testing and General Performance of Coagulation Assays; Approved GuidelineThird Edition (Document H21- A3*). Wayne, PA:NCCLS; 1998].

Low Molecular Weight Heparin (LMWH) Monitoring Practices

Monitoring of LMWH therapy. 14% (n = 82) reported monitoring LMWH therapy.

Assays used*
- 72% (n =47) reported using an aPTT assay.
- 53% (n = 35) reported using an anti-factor Xa assay.

*To monitor LMWH, the CAP recommends using a chromogenic antifactor Xa and against using an aPTT assay (*Arch Pathol Lab Med*. 1998;122:799-807).

Calibration*
- 74% (n = 28) used different calibration curves for LMWH and unfractionated heparin.
- 42% (n =16) used different calibration curves for each type of LMWH.

*The CAP has recommended that laboratories use different calibrations for LMWH and unfractionated heparin (*Arch Pathol Lab Med*. 1998;122:799-807), and establish calibration curves with each lot and type of LMWH (*Arch Pathol Lab Med*. 1998;122:782-798).

Timing of anti-factor Xa assay after administration of LMWH*
32% (n = 12) reported performing anti-factor Xa testing 4 h after injection* while 46% (n = 17) reported not recommending a time for anti-factor Xa testing.

*The CAP recommends that, when LMWH is monitored, the sample be obtained 4 h after subcutaneous injection of LMWH (*Arch Pathol Lab Med*. 1998;122:799–807).

Concluding Remarks

Limitations
Various laboratory practices noted in this survey are those that have been reported; and like any other surveys, they may not reflect actual practices. Surveys are subject to framing biases which can be reduced (e.g., by pilot testing) but not totally avoided.

Generalizability
Due to the high response (79%) and sampling (14%) rates, results of this survey appear to be generalizable.

In conclusion, we found substantial departure from certain accepted coagulation laboratory practices which may result in adverse events. Further studies are necessary to determine to what extent the variability in different coagulation laboratory practices contributes to a change in patient outcomes. There appears to be a need for laboratorians and clinicians to work together to understand the reasons behind these variabilities and to develop concerted efforts to better assure compliance with accepted standards of practice.